

## LETTERS TO THE EDITOR

### Negative antineutrophil cytoplasmic antibodies in Behçet's disease

Sir: Antineutrophil cytoplasmic antibodies have been detected in patients with idiopathic necrotising and crescentic glomerulonephritis, active Wegener's granulomatosis, and microscopic polyarteritis nodosa.<sup>1</sup>

Behçet's disease, an inflammatory disorder of unknown cause, is characterised by oral and genital ulcerations associated with systemic manifestations due to large and small vessel vasculitis. Ocular, cutaneous, and central nervous system involvement are often the translation of small vessel vasculitis.<sup>2</sup> Crescentic glomerulonephritis has also been reported.<sup>3</sup> Polymorphonuclear leucocytes have been incriminated in the physiopathology of Behçet's disease. Lesions are characterised histologically by acute inflammation and an intense infiltration of polymorphonuclear leucocytes with small vessel necrosis, especially at mucosal and cutaneous sites.<sup>4</sup> The increased chemotaxis and random motility of polymorphonuclear leucocytes in Behçet's disease have been confirmed in several studies, and it has been suggested that a cytoplasmic polymorphonuclear leucocyte factor, serum or lymphocytic factor is responsible for this increased activity.<sup>5</sup> To appreciate better the role of polymorphonuclear leucocytes in this disease we looked for the presence of antineutrophil cytoplasmic antibodies in patients with active and inactive Behçet's disease.

Twenty eight patients (27 male, one female) with a mean (SD) age of 40 (3) years (range 29-56) were studied. Disease duration was 6.8 (1.9) years (range 2-25). All patients had buccal aphthosis associated with at least two of the following criteria: genital aphthosis, cutaneous lesions, uveitis, and positive pathergy testing. The incidence of clinical manifestations with reported vasculitis is as follows: uveitis (12 cases), central nervous system disease (six cases), thrombophlebitis (six cases), erythema nodosum-like lesions (five cases), and arterial aneurysm (one case). The disease was active in 15 patients and inactive in 13.

Indirect immunofluorescence on human neutrophils was used to detect antineutrophil cytoplasmic antibodies, according to the method of Van der Woude.<sup>6</sup> None of the 28 serum samples from the patients with Behçet's disease was positive for these antibodies (titres >1/10). The fluorescence was negative in 27 patients and positive in one at a titre of 1/10.

This study strongly suggests that antineutrophil cytoplasmic antibodies cannot be incriminated as contributing to the abnormalities of polymorphonuclear leucocytes in Behçet's disease.

M HAMZA  
Service de Rhumatologie  
Hôpital la Rabta  
Tunis, and  
Faculté Médecine de Tunis  
Tunisia

O MEYER  
Service de Rhumatologie  
Hôpital la Rabta  
Tunis, and  
Faculté de Médecine Xavier Bichat  
Université Paris 7  
Paris

\*Correspondence to: Dr M Hamza, BP 45, El Menzeh 1014, Tunisia.

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### Pregnancy loss, menopause, and the onset of rheumatoid arthritis

Sir: Spector and Silman suggest that spontaneous abortion may have a protective effect on the development of rheumatoid arthritis (RA).<sup>1</sup> This seems at odds with a previous study from the same group reporting that first degree relatives of women with RA who are destined to develop RA themselves have more frequent adverse pregnancy outcomes in the form of perinatal deaths.<sup>2</sup> The authors attempt to reconcile the two studies by suggesting that late reproductive loss is only important in those 'particularly genetically susceptible to rheumatoid arthritis'. Although this is an interesting concept, further information to support this hypothesis has not been obtained. In the first study the obstetric histories of the female probands were not given, yet it may be informative to know how they compared with those reported for their relatives who were either affected or non-affected with RA. In the second study the family histories of the patients with RA were not stated, although presumably some first degree relatives are likely to have RA. A study performed by us supports the findings of the second study. After interviewing a large number of women with RA and other connective tissue disorders we found that pregnancy loss is not a risk factor for the later development of RA.<sup>3</sup>

Undoubtedly, pregnancy loss has an ameliorating effect on the activity of RA. Most women develop RA having completed their pregnancies, however.<sup>3</sup> The influence of other hormonal factors, such as the menopause, deserves more attention. From an interview of 117 women with RA in our previous study it was noticeable that a large number had onset of their arthritis about the time of menopause,

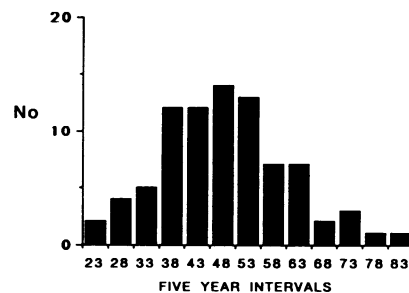


Figure 1 Age of onset of arthritis.

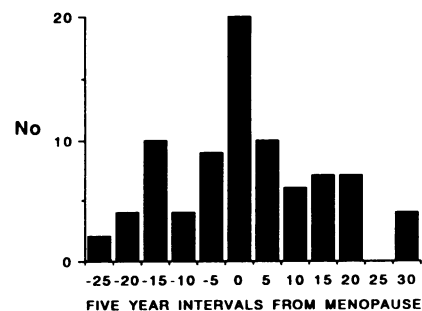


Figure 2 Onset of arthritis in relation to the menopause.

an observation not included in our paper. Age of onset of first symptoms of RA and age at menopause (for this purpose defined as cessation of menses) were obtained from all women at the time of interview, in different sections of a questionnaire, with confirmation by recourse to hospital notes when possible. Seventeen women who had undergone hysterectomy and 17 women who were premenopausal were excluded from this analysis.

There seemed to be a broad peak of age of onset of arthritis coinciding with the expected age of menopause (fig 1). When the onset of arthritis was analysed in relation to the menopause in individual patients there were a larger number reporting onset of arthritis and menopause within an encompassing five year interval (fig 2). Undoubtedly this finding is due partly to an unconscious bias in relating major life events to each other, especially considering our crude definition of the menopause. Nonetheless, it is biologically plausible that hormonal fluctuations occurring during the menopause may trigger onset of RA in some women, perhaps by the same mechanism as that occurring in postpartum flares of arthritis in younger women.

These observations at least merit a prospective study, including appropriate assays for hormonal function in women developing RA. Our epidemiological colleagues may also be able to tell us eventually whether hormone replacement therapy is more advantageous than imagined, or perhaps the opposite.

N J McHUGH  
Royal National Hospital for Rheumatic Diseases  
Upper Borough Walls  
Bath BA1 1RL

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- McHugh N J, Reilly P A, McHugh L A. Pregnancy outcome and autoantibodies in connective tissue disease. *J Rheumatol* 1989; 16: 42-6.

Sir: Dr McHugh makes some interesting points which we would like to consider in turn. It is correctly pointed out that the results of our two studies are at odds with each other with regard to perinatal death and risk of RA. The second study was much larger and had greater power than the first, and was set up to explore the preliminary findings of the initial first study based on RA multicase families. As stated in the paper the results of the family study were based on small numbers of cases and perinatal episodes, and results could not be generalised to the wider sporadic RA population. Although these findings might